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# Mathematical model for describing cerebral oxygen desaturation in patients undergoing deep hypothermic circulatory arrest

**G. W. Fischer*, P. B. Benni†, H.-M. Lin, A. Satyapriya, A. Afonso, G. Di Luozzo, R. B. Griepp and D. L. Reich**

*Department of Anesthesiology and Cardiothoracic Surgery, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1010, New York, NY 10029, USA*

**Corresponding author. E-mail: gregory.fischer@mountsinai.org*

**Background.** Surgical treatment for aortic arch disease requiring periods of circulatory arrest is associated with a spectrum of neurological sequelae. Cerebral oximetry can non-invasively monitor patients for cerebral ischaemia even during periods of circulatory arrest. We hypothesized that cerebral desaturation during circulatory arrest could be described by a mathematical relationship that is time-dependent.

**Methods.** Cerebral desaturation curves obtained from 36 patients undergoing aortic surgery with deep hypothermic circulatory arrest (DHCA) were used to create a non-linear mixed model. The model assumes that the rate of oxygen decline is greatest at the beginning before steadily transitioning to a constant. Leave-one-out cross-validation and jackknife methods were used to evaluate the validity of the predictive model.

**Results.** The average rate of cerebral desaturation during DHCA can be described as: $Sct_{O_2}[t]=81.4-(11.53+0.37\times t)\ (1-0.88\times\exp\ (-0.17\times t))$. Higher starting $Sct_{O_2}$ values and taller patient height were also associated with a greater decline rate of $Sct_{O_2}$. Additionally, a predictive model was derived after the functional form of $a\times\log\ (b+c\times\delta)$, where $\delta$ is the degree of $Sct_{O_2}$ decline after 15 min of DHCA. The model enables the estimation of a maximal acceptable arrest time before reaching an ischaemic threshold. Validation tests showed that, for the majority, the prediction error is no more than $\pm 3$ min.

**Conclusions.** We were able to create two mathematical models, which can accurately describe the rate of cerebral desaturation during circulatory arrest at 12–15°C as a function of time and predict the length of arrest time until a threshold value is reached.

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Surgical treatment for aortic arch disease remains complex and frequently requires periods of circulatory arrest. Despite improved brain protection strategies, this type of cardiac surgery continues to be associated with a spectrum of neuropsychiatric and neurological sequelae.

Deep hypothermic circulatory arrest (DHCA) is an efficacious and commonly used technique in aortic surgery that has been used for more than 30 yr.[1 2] By various mechanisms including reduced metabolic demand, hypothermia enables the brain to survive prolonged periods of circulatory arrest. Unfortunately, the associated morbidity is considerable. Frank stroke rates were recently reported in the range of 6–13%,[3] with more subtle forms of neurocognitive impairment being even higher.[4] Nonetheless, DHCA is an established surgical strategy with marked inter-institutional variability in practice and no universally accepted protocols. For example, the criteria for initiation of circulatory arrest, circulatory arrest duration, and the use of selective cerebral perfusion, retrograde cerebral perfusion, or both differ among institutions considerably.

There is also much heterogeneity regarding patient monitoring for the purposes of circulatory arrest initiation

†*Declaration of interest*. P.B.B. is the chief scientific officer at CASMED, the company that manufactures the FORE-SIGHT®.

and determining its allowable duration. Electroencephalographic (EEG) monitoring, serial measurements of jugular bulb saturations ($Sjv_{O_2}$), and cerebral oximetry based on near-infrared spectroscopy have all been reported to successfully monitor patients for cerebral ischaemia,[5–7] and each is used to guide the initiation of circulatory arrest. However, during DHCA, cerebral oximetry is the only technique that provides contemporaneous information on the ischaemic state of cerebral tissue. The EEG is isoelectric before and during DHCA and cannot differentiate cerebral hypothermia from ischaemia. The no-flow state precludes $Sjv_{O_2}$ measurements. Consequently, cerebral oximetry remains the only technology that can be used in the DHCA setting.

We hypothesized that the observed cerebral tissue oxygen saturation ($Sct_{O_2}$) in patients undergoing aortic arch surgery with DHCA would demonstrate a consistent pattern that can be described by a mathematical relationship that is dependent upon the duration of DHCA.

## Methods

With Institutional Review Board (IRB) approval and informed consent, 36 patients undergoing elective thoracic aortic surgery with DHCA were monitored intraoperatively using the FORE-SIGHT® cerebral oximeter (CAS Medical Systems, Branford, CT, USA) at our institution from 2005 to 2008. Cerebral tissue oxygen saturation ($Sct_{O_2}$) and cerebral tissue haemoglobin (tHB) concentration were continuously recorded.

After the induction of general anaesthesia, two sensors were placed on the subjects' foreheads bilaterally for continuous monitoring of $Sct_{O_2}$. Subjects remained in the supine position during surgery, allowing for only positional changes to facilitate surgical exposure. There was no alteration in surgical technique or routine clinical monitoring.

General anaesthesia was induced in all patients with etomidate, fentanyl, and midazolam. Neuromuscular block was achieved with vecuronium or cisatracurium before tracheal intubation. A balanced anaesthetic technique was used for maintenance consisting of isoflurane (0.6–1.5% end-tidal concentration), fentanyl, vecuronium or cisatracurium, and midazolam. All patients were mechanically ventilated with $F_{I_{O_2}}$ 100% in a pressure-regulated volume-controlled mode so as to maintain the $Pa_{CO_2}$ at 4.6–6.0 kPa.

The following monitoring devices were placed: a left radial arterial catheter, a pulmonary artery catheter inserted via the right internal jugular vein, a 20 G jugular bulb catheter for intermittent sampling of jugular venous blood, and a urinary bladder catheter with an integrated temperature thermistor (to measure core temperature). Additionally, nasopharyngeal temperature was measured in all patients.

The jugular bulb catheter was inserted into the internal jugular vein under ultrasonic vessel guidance. The catheter was advanced using the Seldinger technique to a maximal length of 10–12 cm. A baseline measurement was obtained to confirm proper placement (oxyhaemoglobin saturation <70%). Saturations higher than 70% were believed to represent a malpositioned catheter (e.g. facial vein), requiring an additional attempt at proper placement. Once a bladder temperature of 20°C was reached, serial $Sjv_{O_2}$ measurements were performed every 5 min. After obtaining at least one $Sjv_{O_2}$ measurement >94%, with a total cooling time of at least 45 min, DHCA commenced. Nasopharyngeal arrest temperatures ranged between 12°C and 15°C.

The technique of DHCA used at our institution was consistent throughout the study and has been described in detail previously.[8 9]

Two subsets of patients presenting for elective thoracic aortic arch surgery were included in this study. The first population required replacement of the entire aortic arch. The technique utilized is described in detail by Spielvogel and colleagues.[8] Briefly, CPB is achieved by cannulation of the right axillary artery and venous drainage through a two-stage cannula placed into the right atrium. After CPB is commenced, patients are cooled down to a nasopharyngeal temperature of 12–15°C utilizing α-stat management. Ischaemic DHCA is commenced once the abovementioned criteria are fulfilled. During circulatory arrest, a trifurcated graft is sewn to the head vessels. Once all three anastomoses are completed, the graft is deaired and the proximal end clamped. Via the right axillary artery, selective antegrade cerebral perfusion (SCP) is started (10 ml $kg^{-1}$ ideal body weight $min^{-1}$) after 15–45 min of ischaemic DHCA. During SCP, a tube graft is used to connect the non-diseased portion of the ascending aorta with the proximal end of the descending aorta. Subsequently, the trifurcated graft is sewn to the aortic tube graft. After meticulous deairing, total body perfusion is commenced and the patient rewarmed.

The other group consisted of patients presenting for repair of the ascending aorta with a beveled suture line at the arch (hemiarch procedure). This technique is described by Etz and colleagues[9] in detail. Briefly, CPB technique and temperature management on bypass are identical as described for total aortic arch replacement. The proximal anastomosis is performed with the aorta cross-clamped. Once completed and all arrest criteria fulfilled (temperature 12–15°C, $Sjv_{O_2}$ >94%, and a minimal cooling time of 45 min), circulatory arrest is commenced for suturing of the distal anastomosis. Once completed, total body circulation is resumed and the patient rewarmed. No SCP is required for this technique.

Hence, it is important to note that all patients received ischaemic DHCA without supplemental cerebral perfusion enabling us to model the decline of $Sct_{O_2}$ during the time of arrest.

### *Modelling and statistical analysis*

$Sct_{O_2}$ and total haemoglobin concentration in tissue (tHB) data were recorded every 2 s, along with subject characteristic information from our institution's Anesthesia Information Management System (AIMS) (Compurecord, Philips Medical Systems, Andover, MA, USA). Each subject's left and right sensor $Sct_{O_2}$ data were averaged together for each event. For analysis, the median $Sct_{O_2}$ from each minute, rounded by 0.25, was used, and the first data point of the same $Sct_{O_2}$ value was used.

To determine the rate of $Sct_{O_2}$ decline during DHCA, a non-linear mixed model was fit for the $Sct_{O_2}$ physiological model based on the individual appearance of the $Sct_{O_2}$ decline during DHCA. The model assumes that the rate of oxygen decline is greatest at the beginning before steadily converging to a constant (so the trend of $Sct_{O_2}$ becomes linear after a certain time point). For each subject $i$, the $Sct_{O_2}$ at time $t>0$ ($Sct_{O_2}[t]$) is:

$$Sct_{O_2}[t] = Sct_{O_2}[0] - (\beta_0 + \beta_1 \times t + b_i)(1 - \lambda \times \exp(-(\kappa + \gamma_i) \times t)) + e[t]_i \quad (1)$$

where $Sct_{O_2}[0]$ is the initial $Sct_{O_2}$, and $(\beta_0+\beta_1\times t+b_i)(1-\lambda\times\exp(-(\kappa+\gamma_i)\times t))$ is the model describing the degree of $Sct_{O_2}$ decline over time. As time $t$ increases, the term $1-\lambda\times\exp(-(\kappa+\gamma_i)\times t)$ converges to 1, leaving the model to be affected only by the linear component $(\beta_0+\beta_1\times t+b_i)$. In other words, $1-\lambda\times\exp(-(\kappa+\gamma_i)\times t)$ modulates when the $Sct_{O_2}$ decline changes from the exponential trend to the linear trend. The coefficient $\beta_1$ is the decline rate thereafter.

Note that in the non-linear mixed model in equation (1), $\beta_0$, $\beta_1$, $\lambda$, and $\kappa$ are the population parameters that characterize the overall trajectory of $Sct_{O_2}$, whereas $b_i$ and $\gamma_i$ are the random components which allow each individual to have his/her own intercept ($b_i$) and scale parameter ($\gamma_i$) deviated from the population averages $\beta_0$ and $\kappa$. The two random variables $b_i$ and $\gamma_i$ were assumed to have a bivariate normal distribution with mean zeros and a covariance structure with unspecified mathematical form. Compared with the population average, a positive $b_i$, $\gamma_i$, or both correspond to a greater decline rate before reaching to the linear phase, and a positive $b_i$ also corresponds to a more significant total reduction of $Sct_{O_2}$ at the end. The data, however, did not suggest random slopes among individuals based on the Akaike information criterion, a statistic used for choosing among models.[10] This implies that the final decline rate is similar across all subjects. The residual errors at time $t$, that is, $e[t]_i$, were assumed to be independent and identically normally distributed.

Additionally, a predictive model was derived enabling clinicians to estimate the maximal acceptable DHCA time that can pass before reaching an ischaemic threshold. Since the aforementioned physiological model has an exponential component, it is natural to use a logarithmic function to predict the DHCA time given a pre-specified $Sct_{O_2}$ value. Specifically, the DHCA time will be predicted using the following functional form:

$$\text{DHCA time}[t] = a \times \text{LN}(b + \exp(c) \times \delta) \quad (2)$$

where LN is the natural logarithm function, and $\delta$ is the difference between the $Sct_{O_2}$ at 15 min and the pre-specified $Sct_{O_2}$ threshold (i.e. $\delta = Sct_{O_2}[15] - Sct_{O_{2thres}}[t]$). Because the coefficient of $\delta$ tended to be small, to increase the stability of the modelling process, and to ensure that a larger decline is associated with a longer time, an exponential function for the coefficient of $\delta$ was used.

Similar to the physiological model, we allowed individual baseline characteristics to influence *a, b*, and *c* in equation (2) of the predictive model. The potential predictors for each of *a, b*, and *c* included age (yr), height (cm), gender, pre-arrest haematocrit (%), core temperature (°C), pH, $Pa_{CO_2}$ (mm Hg), $Pa_{O_2}$ (mm Hg), the $Sct_{O_2}$ value at 10 min after the onset of DHCA ($Sct_{O_2}[10]$), and the rate of $Sct_{O_2}$ decline between 5 and 10 min (i.e. $r_{[5,10]} = (Sct_{O_2}[5] - Sct_{O_2}[10])/5$).

As a first step, we fitted a full model including all of the potential predictors. Because gender, core temperature (°C), pH, $Pa_{CO_2}$(kPa), and $Pa_{O_2}$ (kPa) were not close to reaching statistical significance ($P>0.5$), the list was further reduced by omitting them altogether. The final model was obtained based on manual elimination of the least significant predictor one at a time (akin to the backward selection method) until all of the remaining predictors had $P<0.05$.

Leave-one-out cross-validation and jackknife resampling were performed to assess the prediction error and bias of the parameter estimates of the predictive model.[11] Both methods involve omitting one subject at a time and remodelling on the remaining subset using the same set of predictors. In leave-one-out cross-validation, we computed the predicted values across various time points of the left-out subject based on the model without that subject, and then calculated the mean square error and the mean absolute error for that subject. The mean square (absolute) error is the average squared (absolute) difference between the observed and the predicted values. Since there were only 30 subjects with more than one observation in the time period after 15 min of DHCA onset, this was repeated 30 times leaving out one subject at a time. The final prediction error was defined as the average (or median) of these 30 individual prediction errors. In jackknife, the medians (because of the small sample size, we chose to use the median) of the parameter estimates were compared with those estimated from the predictive model. The jackknife bias is the (number of validations−1) times the differences of these two estimates.

All statistical analysis was carried out using SAS v9.1 (SAS Institute, Inc., Cary, NC, USA), and PROC NLMIXED was used to develop the physiology and time

**Table 1** Patient characteristics

| Variable | Mean | SD | Min. | Median | Max. |
|---|---|---|---|---|---|
| Weight (kg) | 83.50 | 22.48 | 45.00 | 80.50 | 136.00 |
| Height (cm) | 174.94 | 9.76 | 155.00 | 178.00 | 193.00 |
| Body surface area ($m^2$) | 1.99 | 0.31 | 1.42 | 1.96 | 2.62 |
| Age (yr) | 67.97 | 11.60 | 42.00 | 68.00 | 89.00 |
| Male | 67% | | | | |
| Pre-arrest haematocrit (%) | 25.58 | 4.17 | 16.00 | 25.50 | 36.00 |
| Temperature at arrest (°C) | 13.64 | 1.86 | 10.50 | 13.50 | 17.70 |
| pH | 7.35 | 0.06 | 7.22 | 7.35 | 7.45 |
| $Pa_{co_2}$ (kPa) | 5.8 | 0.9 | 4.2 | 5.7 | 8.0 |
| $Pa_{o_2}$ (kPa) | 47.3 | 14.4 | 27.4 | 44.2 | 92.9 |

predictive models. The level of statistical significance for hypothesis testing was set to be 0.05. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

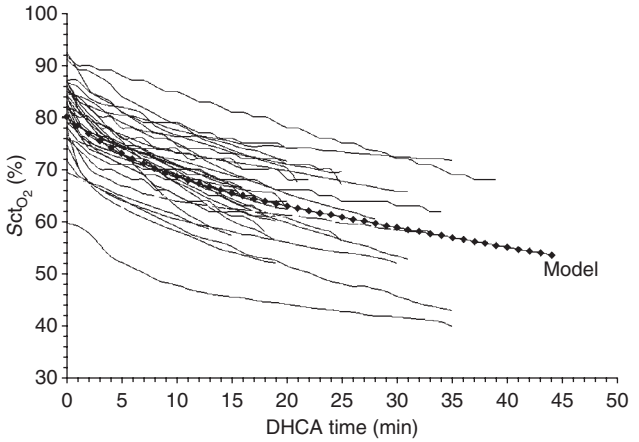


**Fig 1** Physiology model of cerebral tissue oxygen saturation ($Sct_{o_2}$) as a function of time superimposed over the individualized subject $Sct_{o_2}$ recordings during DHCA.

## Results

Thirty-six subjects completed the study (Table 1). The study population consisted of 25 males and 11 females. The patients were 28 Caucasian, two African American, one Asian, and five Hispanics. The patients' age ranged from 42 to 89 yr, weight 45–136 kg, and height 155–193 cm. Twenty-two subjects underwent replacement of the ascending aorta including hemiarch replacement, whereas 14 subjects received total aortic arch replacements.

The individual profiles and the model curve are presented in Figure 1. The mean post-induction $Sct_{o_2}$ value for the 36 subjects was 70.9% (SD 4.9%). In general, median $Sct_{o_2}$ values increased proportionally during the pre-DHCA period as temperature decreased. Once a nasopharyngeal temperature of 12–15°C was reached, the average $Sct_{o_2}$ value was recorded at 81.4% (SD 6.6%). DHCA was now commenced. During DHCA, a decline in mean $Sct_{o_2}$ values was seen [$DHCA_{+10\ min}$ 68.8% (SD 7.4%, $n$=36), $DHCA_{+20\ min}$ 64.9% (SD 8.0%, $n$=21), and $DHCA_{+30\ min}$ 58.2% (SD 10.3%, $n$=10)]. After DHCA ended and cerebral perfusion was reinstituted, $Sct_{o_2}$ usually increased to pre-DHCA onset values [End $DHCA_{+15\ min}$ 79.0% (SD 9.6%)]. During rewarming, $Sct_{o_2}$ returned to near post-induction values [$DHCA_{end}$ 69.2% (SD 6.9%)].

### *Physiological model*

As can be seen from the model curve (Fig. 1), $Sct_{o_2}$ decreased rapidly at first before gradually transitioning to a more linear decline. The non-linear mixed model in equation (1) showed that the mean initial $Sct_{o_2}$ value was 81.4% (95% CI: 79.26–83.58%), the mean intercept and slope ($\beta_0$ and $\beta_1$) in the linear component were 11.53 (9.94–13.12) and 0.37 (0.34–0.40), respectively; and the mean shape and scale parameters ($\lambda$ and $\kappa$) in the exponential component were 0.17 (0.16–0.19) and 0.88 (0.87–0.90), respectively. Thus, the population curve can be

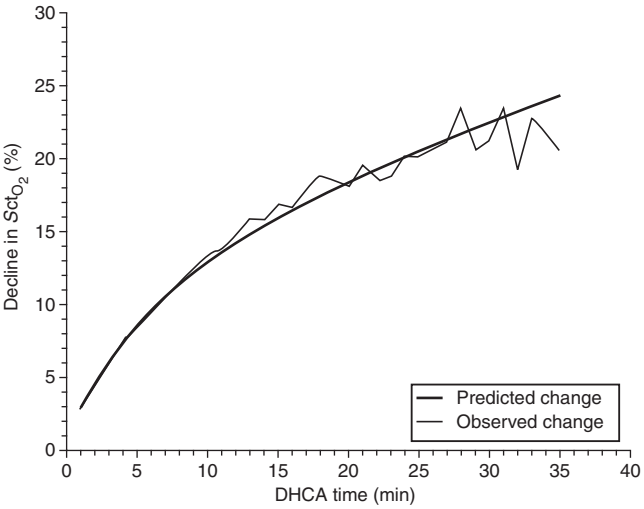


**Fig 2** Observed and predicted values of the physiology model showing the amount of cerebral tissue oxygen saturation ($Sct_{o_2}$) decline as a function of time.

approximated to:

$$Sct_{O_2}[t] = 81.4 - (11.53 + 0.37 \times t)(1 - 0.88 \times \exp(-0.17 \times t)) \quad (3)$$

Figure 2 shows the estimated changes, compared with the observed, from the above model for the 35 min period after commencement of DHCA. On the basis of the model, the estimated decline rates per minute at 5, 10, 15, 20, 25, and 30 min were 1.14%, 0.75%, 0.55%, 0.45%, 0.41%, and 0.39%, respectively. The asymptote of the $Sct_{o_2}$ decline rate was estimated to be 0.37% per minute (0.34–0.40). Furthermore, this final decline rate appeared to be fairy similar across subjects (data not shown); however, there was substantial between-subject variability for the initial $Sct_{o_2}$ declines [standard deviations of $b_i$ and

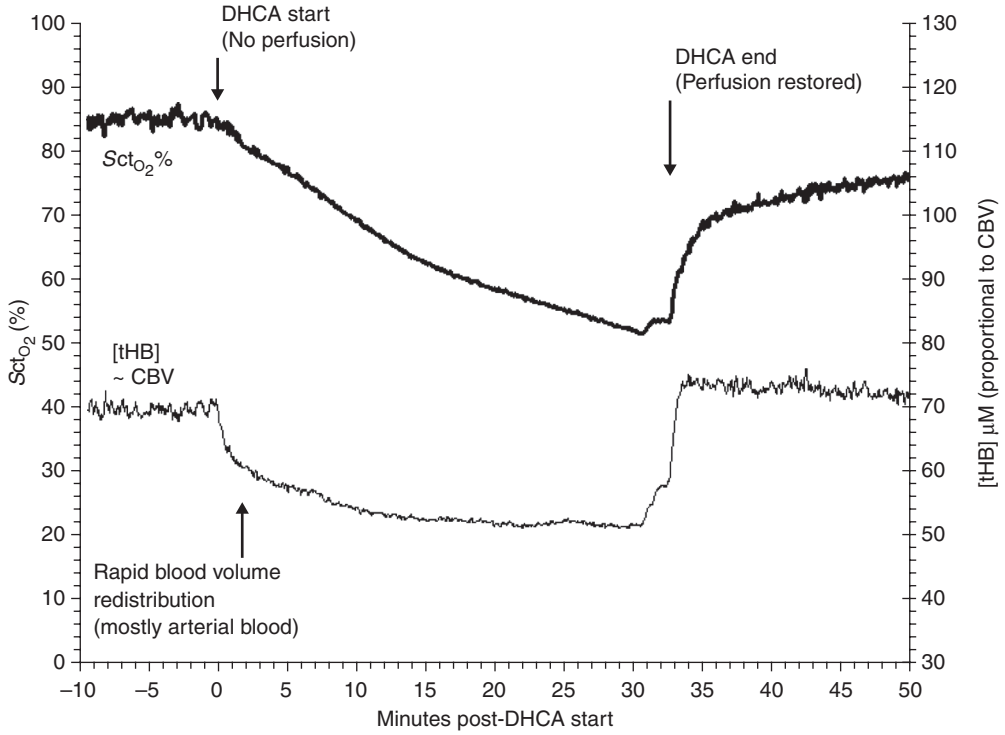


**Fig 3** Cerebral tissue oxygen saturation ($Sct_{O_2}$) and tHb measured by NIRS during the DHCA period to show initial rapid cerebral blood volume depletion under sensor before levelling off. During this period, tHb is proportional to CBV assuming that the blood haemoglobin level is constant.

$\gamma_i$ in equation (1) are 6.9% and 0.14%)]. Finally, after taking into account the individual differences (i.e. allowing random effects $b_i$ and $\gamma_i$), the standard deviation of the error term $e[t]_i$ in equation (1) is 0.60%, compared with 4.0% without the random effects.

To assess whether characteristics at baseline could explain the individual differences in $Sct_{O_2}$ trajectories after DHCA onset, we modelled them by allowing baseline and patient characteristics data to influence $\beta_0$ and $\kappa$. It appeared that higher initial value $Sct_{O_2}[0]$ and taller height (both $P<0.01$) were associated with a greater decline rate. Furthermore, taller height was also associated with a more significant final reduction of $Sct_{O_2}$ ($P<0.01$). Subsequently, the alternative population physiology model can be shown as:

$$Sct_{O_2}[t] = 81.4 - (\beta_0 + 0.37 \times t)(1 - 0.88 \times \exp(-\kappa \times t)) \quad (4)$$

where $\beta_0=11.54+0.18\times(\text{height}-175)$ and $\kappa=0.16+0.002\times(Sct_{O_2}[0]-80)+0.002\times(\text{height}-175)$, where $Sct_{O_2}[0]$ and height were centred near their sample means: 80% and 175 cm, respectively.

In addition to $Sct_{O_2}$ the FORE-SIGHT® cerebral oximeter also measures total tHB. Figure 3 demonstrates the reduction in tHB seen in the initial phase of DHCA. After 10–15 min of initial steep decline, the tHB curve tended to flatten out. A return to baseline was then seen once circulation to the brain was resumed.

### *Predictive model for time to ischaemic threshold*

The physiological model describes the time course of $Sct_{O_2}$ during DHCA, but to put into practice, we developed a logarithmic model for clinicians to predict the safe DHCA time before passing an ischaemic threshold.

Taking $\delta$ as the difference between $Sct_{O_2}$ at 15 min and the pre-specified $Sct_{O_2}$ threshold (i.e. $\delta=Sct_{O_2}[15]-Sct_{O_{2thres}}[t]$), then the final DHCA time predictive model is:

$$\text{DHCA time}[t] = a \times \text{LN}(b + \exp(c) \times \delta) \quad (5)$$

where $a=22.15-0.06\times(Sct_{O_2}[10]-70)+5.43\times r_{[5,10]}-0.53\times(\text{height}-175)$, $b=1.70+0.01\times(\text{height}-175)$, and $c=0.173-2.09\times r_{[5,10]}+0.06\times(\text{height}-175)$.

The predictive model only identified height, $Sct_{O_2}$ value at 10 min ($Sct_{O_2}[10]$), and the rate of $Sct_{O_2}$ decline between 5 and 10 min as significant predictors (Table 2). Similar to the physiological model, no other baseline characteristic was found to make an additional contribution.

To illustrate how this model can be utilized to predict the time until a threshold is reached, consider the following hypothetical example.

DHCA commenced 10 min ago for a patient whose height is 170 cm, and showed an $Sct_{O_2}$ value of 68% at 10 min, with a decline rate between 5 and 10 min of 0.8% per minute. The anaesthesiologist would like to predict the time until the threshold value of 60% is reached. On the basis of the physiology model, the decline rate for the

**Table 2** Parameter estimates and its robustness of the predictive model. *The jackknife coefficient is the median of the 30 coefficients from the cross-validations. †The jackknife bias is calculated as the (number of validations−1) times the difference between the two coefficients from the model and the jackknife results. Appearance (%), percentage of times that the predictors were selected as statistically significant ($P<0.05$) in the 30 cross-validation analyses

| Predictor | Proposed predictive model | | | Jackknife results | | Appearance (%) in 30 cross-validations as $P<0.05$ |
|---|---|---|---|---|---|---|
| | Coeff. | SE | *P*-value | Coeff.* | Bias† | |
| *a* | | | | | | |
| Intercept | 22.15 | 7.76 | <0.01 | 22.11 | −1.16 | 97% |
| $Sct_{O_2}$[10] (%) | −0.06 | 0.03 | 0.02 | −0.06 | <0.01 | 93% |
| $r_{[5,10]}$ (% min$^{-1}$) | 5.43 | 2.10 | 0.01 | 5.42 | −0.55 | 93% |
| Height (cm) | −0.53 | 0.17 | <0.01 | −0.53 | <0.01 | 90% |
| *b* | | | | | | |
| Intercept | 1.70 | 0.25 | <0.01 | 1.70 | 0.07 | 100% |
| Height (cm) | 0.01 | 0.01 | 0.02 | 0.01 | <0.01 | 90% |
| *c* | | | | | | |
| Intercept | 0.17 | 0.70 | 0.81 | 0.17 | 0.05 | 0% |
| $r_{[5,10]}$ (% min$^{-1}$) | −2.09 | 0.27 | <0.01 | −2.09 | −0.03 | 100% |
| Height (cm) | 0.06 | 0.01 | <0.01 | 0.06 | −0.20 | 90% |

10–15 min after the commencement of DHCA is observed to be 0.6% per minute on average. Thus, assume that the $Sct_{O_2}$ will be 65% at 15 min, then $a=22.15-0.06\times(68-70)+5.43\times(0.8)-0.53\times(170-175)=29.26$, $b=1.70+0.01\times(170-175)=1.65$, and $c=0.173-2.09\times(0.8)+0.06\times(170-175)=-1.80$.

Therefore, the estimated safe DHCA time being $29.26\times\text{LN}(1.65+\exp(-1.80)\times(65-60))=26.5$ min since the onset of DHCA or 11.5 additional minutes after $DHCA_{+15\ min}$. Similarly, if the $Sct_{O_2}$ threshold is chosen to be 55%, then the estimated time is 35.0 min since the onset of DHCA.

### *Model validation*

We used the leave-one-out cross-validation and the jackknife resampling method to assess the validity of this model, which involved eliminating one subject at a time and re-fitted the model using the same set of parameters as those proposed above. There were 30 cross-validations because only 30 subjects had more than one observation 15 min after DHCA onset. The accuracy of the parameter estimates was assessed by the consistency between the parameter estimates from the predictive model and the jackknife estimates. The jackknife bias, in general, was negligible. The robustness of a predictor was assessed by the percentage of times the predictor was statistically significant (defined as $P<0.05$) (Table 3). All of the predictors, except the intercept for *c*, were statistically significant in at least 73% of the cross-validations.

The predictive strength of the model was assessed by the prediction error. For each cross-validation, we calculated the average of the *absolute* and the *squared* differences between the observed and the predicted observations of the subject who was left out (mean absolute error and mean square error). Overall, the median of the mean absolute error across the 30 cross-validations was 1.56 min, and the average was 1.93 min. The median (interquartile range) of the mean square error was 3.42 min, and the average was 7.06 min which was slightly larger due to one extreme outlier. Summary of the prediction error, overall and also stratified by $Sct_{O_2}$ values (in every 5% increment), is presented in Table 3. Figure 4 also shows the residuals for these 30 subjects. The results indicate that, for the majority, the prediction error is no more than $\pm 3$ min. As expected, prediction will become less accurate once $Sct_{O_2}$ values decrease beneath 50.

**Table 3** Prediction error from the 30 cross-validations

| $Sct_{O_2}$ range during DHCA | Prediction error | Mean | Median | 25th pctl | 75th pctl |
|---|---|---|---|---|---|
| Overall | Mean absolute error | 1.93 | 1.56 | 0.73 | 3.21 |
| | Mean square error | 7.06 | 3.42 | 0.59 | 12.35 |
| −50 | Mean absolute error | 3.34 | 3.88 | 0.89 | 5.25 |
| | Mean square error | 17.06 | 15.75 | 1.22 | 34.21 |
| 50–55 | Mean absolute error | 2.28 | 2.12 | 0.87 | 3.69 |
| | Mean square error | 7.69 | 5.91 | 1.04 | 14.34 |
| 55–60 | Mean absolute error | 1.97 | 0.97 | 0.59 | 3.25 |
| | Mean square error | 8.44 | 0.95 | 0.49 | 13.16 |
| 60–65 | Mean absolute error | 1.39 | 1.62 | 0.49 | 2.00 |
| | Mean square error | 3.30 | 3.51 | 0.32 | 4.40 |
| 65–70 | Mean absolute error | 1.72 | 1.12 | 0.40 | 2.21 |
| | Mean square error | 7.11 | 2.04 | 0.16 | 4.88 |
| 70–75 | Mean absolute error | 2.55 | 2.18 | 1.58 | 3.87 |
| | Mean square error | 9.17 | 6.18 | 2.62 | 17.74 |

## Discussion

DHCA is a commonly used strategy in aortic arch surgery. Institutional protocols are variable and are mostly based on anecdotal or animal-model experiences. As a result, generalized protocols have been developed, not taking into account the inter-individual variability among patients, which ultimately results in persistently high morbidity rates even when these protocols are followed correctly.[3]

Cerebral oximetry is currently the only readily available monitoring modality that can provide the clinician with contemporaneous information on the ischaemic state of cerebral tissue in the operating room setting. Consequently, the mathematical models presented in this manuscript will enable clinicians to individualize and adjust DHCA strategies to the requirements of the individual patient and not vice versa. The ability to forewarn the surgeon (e.g. 10 min of safe circulatory arrest time left) will allow for alternative cerebral perfusion strategies to be implemented if the intended procedure cannot be completed within the allotted time frame (e.g. selective cannulation of head vessels, perfusion of the right vertebral artery and right carotid artery with collateralization via the circulus of Willis, etc.).

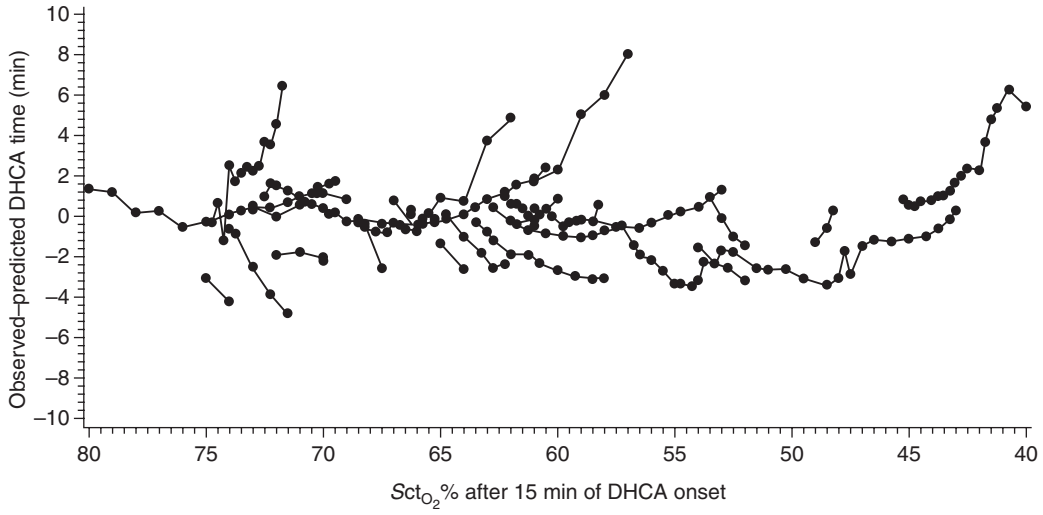


**Fig 4** Residual spaghetti plots demonstrating the magnitude of the individual residuals in our data set. Each line represents a patient. Note that for the majority of patients, the residuals lie within $\pm 3$ min.

The mathematical formula we present demonstrates that cerebral desaturation follows a two-compartment model, similar to the one that many drugs follow in pharmacokinetics. A reasonable explanation for this model can be found by investigating the redistribution of blood volume within the cranial vault once circulatory arrest commences. Near-infrared spectroscopy (NIRS) monitors are capable of measuring not only cerebral tissue oxygenation but haemoglobin concentration per volume of tissue (units: micromoles Hb litre$^{-1}$ or 1000 cm$^3$ of tissue, abbreviated $\mu$M) as well.[12–15] It is important to note that total tHB should not be confused with conventional haemoglobin concentration measurements (HGB) in blood, measured in g dl$^{-1}$. Cerebral blood volume is proportional to tHB divided by blood haemoglobin within the cranial vault.

Figure 3 demonstrates the reduction in tHB seen in the initial phase of DHCA, which we believe explains the exponential decline in $Sct_{O_2}$ seen in the initial 10–15 min of the physiological model. In other words, the initial exponential decline in $Sct_{O_2}$ is a function of both blood volume redistribution and ongoing tissue metabolism. After 10–15 min, the gravitational redistribution of intracranial blood away from the oximetry sensors, which are attached to the subject's forehead, is mostly completed. Subsequently, only ongoing tissue metabolism is seen resulting in the second linear phase of our model.

The time predictive model is flexible, enabling a threshold value under which cerebral ischaemia is believed to occur to be arbitrarily selected by the perioperative care provider (e.g. $Sct_{O_{2thres}}$=60% or 50%). This model was developed specifically with the intent to predict the time necessary before reaching an ischaemic threshold only in the time period beyond 15 min after commencement of DHCA. Data acquired during the first 10 min of circulatory arrest is used to improve the predictive strength of the model. The $Sct_{O_2}$ data acquired during the time interval, 10 to 15 min, were intentionally not included enabling the model to provide the clinician with a 5 min warning before reaching the selected threshold. We justify this approach based on our institution's long-standing history of utilizing DHCA as a primary strategy for addressing pathologies of the aortic arch. With the use of extreme hypothermia, we believe that cerebral metabolism is adequately suppressed, making adverse neurological outcomes highly unlikely when arrest times are kept under 15 min.

The model described is based on the subject being in the supine position undergoing deep hypothermia with nasopharyngeal temperatures at 12–15°C. If milder hypothermia is used during circulatory arrest, as is used in many other institutions, a higher rate of $Sct_{O_2}$ desaturation is expected due to higher tissue metabolism. If the subject's head is in a position other than supine, the redistribution of blood volume under the cerebral oximetry sensors may be different from the data used to create this model.

Owing to the small number of subjects included in this study and the fact that only the period of circulatory arrest was investigated, an association between $Sct_{O_2}$ values and clinical outcome cannot be made, because decreased $Sct_{O_2}$ events outside of the DHCA period will also contribute to clinical outcome.

Although it would have been ideal to validate the predictive model utilizing new subjects, the difficulty in obtaining an adequate same sample size would have surely resulted in statistical non-significance. Consequently, we used leave-one-out cross-validation and the jackknife resampling method to assess the validity of the predictive model.

A further shortcoming of this study is that the ischaemic threshold value under which an increase in adverse events will be seen is unknown. The strength of our predictive

model lies in its flexibility. The clinician can freely choose a threshold value. As further research is conducted in the field of absolute cerebral oximetry, we hope that a threshold value will be defined.

In conclusion, cerebral oximetry provides information on the availability of oxygen in brain tissue at risk during numerous pathological conditions.[7] We present a mathematical model that can aid the clinician in determining the length of DHCA that can be undertaken safely and can be utilized to define the safest time point to commence DHCA. To date, there is insufficient evidence present to recommend a specific absolute threshold under which significantly more adverse events are appreciated. Consequently, the present study must be considered a preliminary investigation. Ultimate model validation should be performed in a prospective study. Owing to the complexity and relative rarity of this procedure, a multicenter trial will most likely be required, which in addition could potentially correlate threshold values with outcomes.

## Funding

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